

REMARKS

This paper is responsive to the Final Office Action of August 5, 2008.

I. *Claim Status*

Claims 1-20 are pending in the application. These claims have been rejected. Claim 1 has been amended to clarify the invention. No new matter is added.

II. *Rejections Under 35 U.S.C. § 103*

Claims 1-20 stood rejected under 35 U.S.C. § 103(a) as being unpatentable over (1) WO - A- 95 10514 (“WO 95”); (2) Iwasaki et al., 1999, Chemical And Pharmaceutical Bulletin, JP (11-1999), Vol.42, pages 2285-2290 (“Iwasaki”); (3) Sejas et al., 1998, Tetrahedron, 44:6197-6200 (“Sejas”); (4) WO-A-9631478 (“WO 96”), (5) EP 0,208,855 (“EP ‘855”), (6) EP 0,152,897 (“EP ‘897”), (7) US 4,659,716 (“716 patent”), or (8) HU 194,864 (“HU ‘864”) independently and also all in view of Peon et al., 2002, J. Am. Chem. Soc. 124:6428-6438 (“Peon”).

Applicant respectfully traverses this rejection.

At page 2 of the Office Action, the Examiner noted that “[t]he arguments are not found to be persuasive. Applicants are arguing the Peon Jorge et al reference. It should be noted that the examiner has made the rejections independently. The Peon reference is used just to validate the point even further.” In response, Applicant respectfully requests the Examiner to refer to the first office action of June 27, 2007 and the Applicant’s response of September 25, 2007. In the first Office Action, the Examiner noted that ‘the above prior art [i.e., the prior art numbers (1) to (8) above] disclose the process of making DCL in the presence of aqueous alcohol and a base.’ Applicant’s response was that the references cited by the Examiner thus show a clear pattern for producing Desloratadine (or DCL) by reacting loratadine with an aqueous alcohol and/or non-alcoholic solvents. The Examiner made certain conclusory statements with regard to the use of neat alcohol in place of aqueous alcohol and in this connection referred to the Peon et al., reference. Applicant responded to this aspect of the rejection too as set forth in the response of September 25, 2007 and in the response of April 21, 2008. Notwithstanding, Applicant respectfully submits again that the Examiner failed to establish the *prima facie* case of

obviousness for at least the following reasons:

A. Discussion of Rejections Independently

(1) WO 95

The WO 95 reference discloses a process for making DCL in the presence of aqueous alcohol. The WO 95 reference, however, does not disclose or suggest a process for the production of desloratadine by reacting loratadine with neat alcohol in presence of an inorganic base. The Examiner failed to establish a *prima facie* case of obviousness based on the WO 95 reference. Specifically, the Examiner has not provided a sufficient reason or explicit analysis of why a person of ordinary skill has a reason to pursue neat alcohol in place of aqueous alcohol in a process for making DCL as claimed by the Applicant. Mere conclusory statements such as “[i]t is known that neat alcohol would be more reactive and efficient than an aqueous solvent . . . The proton transfer is from a neat alcohol is known to faster” are not sufficient. There must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” *In re Kahn*, 441 F. 3d 977 (Fed. Cir. 2006). Indeed, there is evidence to the contrary: (i) a clear pattern exists in the art for producing DCL by reacting loratadine with an aqueous alcohol and/or non-alcoholic solvents as evidenced by a number of references cited by the Examiner; and (ii) the proton transfer is faster (in 3 ps or “2 orders of magnitude” higher) in “aqueous” environment, than in “neat alcohol” (see, Peon at 6436 and Table 2 at 6435) (and hence “aqueous make[s] the fuel cell more efficient and faster”).

In view of this evidence, a person of ordinary skill having the WO 95 reference in hand has no good reason to pursue neat alcohol in place of aqueous alcohol in a process for making DCL and such a pursuit would not lead to the anticipated success. Reconsideration and withdrawal of the rejection based on WO 95 are respectfully requested.

(2) Iwasaki

The Iwasaki reference is related to different tricyclic antihistamine derivatives and not related to desloratadine preparation from loratadine, and it does not disclose or suggest a process for the production of desloratadine by reacting loratadine with neat alcohol in presence of an

inorganic base. The Examiner failed to establish a *prima facie* case of obviousness based on the Iwasaki reference. Specifically, the Examiner has not provided a sufficient reason or explicit analysis of why a person of ordinary skill has a reason to pursue neat alcohol in place of aqueous alcohol in a process for making DCL as claimed by the Applicant. Mere conclusory statements such as “[i]t is known that neat alcohol would be more reactive and efficient than an aqueous solvent . . . The proton transfer is from a neat alcohol is known to faster” are not sufficient. There must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” *In re Kahn*, 441 F. 3d 977 (Fed. Cir. 2006). Indeed, there is evidence to the contrary: (i) a clear pattern exists in the art for producing DCL by reacting loratadine with an aqueous alcohol and/or non-alcoholic solvents as evidenced by a number of references cited by the Examiner; and (ii) the proton transfer is faster (in 3 ps or “2 orders of magnitude” higher) in “aqueous” environment, than in “neat alcohol” (see, Peon at 6436 and Table 2 at 6435) (and hence “aqueous make[s] the fuel cell more efficient and faster”).

In view of this evidence, a person of ordinary skill having the Iwasaki reference in hand has no good reason to pursue neat alcohol in place of aqueous alcohol in a process for making DCL and such a pursuit would not lead to the anticipated success. Reconsideration and withdrawal of the rejection based on Iwasaki are respectfully requested.

(3) Sejas

The Sejas reference is related to dicarbonyl coupling reaction between tricyclic ketones and cyclic ketones and not related to desloratadine preparation from loratadine, and it does not disclose or suggest a process for the production of desloratadine by reacting loratadine with neat alcohol in presence of an inorganic base. The Examiner failed to establish a *prima facie* case of obviousness based on Sejas. Specifically, the Examiner has not provided a sufficient reason or explicit analysis of why a person of ordinary skill has a reason to pursue neat alcohol in place of aqueous alcohol in a process for making DCL as claimed by the Applicant. Mere conclusory statements such as “[i]t is known that neat alcohol would be more reactive and efficient than an aqueous solvent . . . The proton transfer is from a neat alcohol is known to faster” are not sufficient. There must be some articulated reasoning with some rational

underpinning to support the legal conclusion of obviousness.” *In re Kahn*, 441 F. 3d 977 (Fed. Cir. 2006). Indeed, there is evidence to the contrary: (i) a clear pattern exists in the art for producing DCL by reacting loratadine with an aqueous alcohol and/or non-alcoholic solvents as evidenced by a number of references cited by the Examiner; and (ii) the proton transfer is faster (in 3 ps or “2 orders of magnitude” higher) in “aqueous” environment, than in “neat alcohol” (see, Peon at 6436 and Table 2 at 6435) (and hence “aqueous make[s] the fuel cell more efficient and faster”).

In view of this evidence, a person of ordinary skill having the Sejas reference in hand has no good reason to pursue neat alcohol in place of aqueous alcohol in a process for making DCL and such a pursuit would not lead to the anticipated success. Reconsideration and withdrawal of the rejection based on Sejas are respectfully requested.

(4) WO 96

The WO 96 reference discloses a process for making DCL. In particular, the WO 96 reference is related to desloratadine preparation from loratadine by acidic hydrolysis using HCl, HBr, H₂SO₄ and trifluoroacetic acid in different solvents such as dioxane, methylenedichloride, acetic acid, etc. The WO 96 reference, however, does not disclose or suggest a process for the production of desloratadine by reacting loratadine with neat alcohol in presence of an inorganic base. The Examiner failed to establish a *prima facie* case of obviousness based on the WO 96 reference. Specifically, the Examiner has not provided a sufficient reason or explicit analysis of why a person of ordinary skill has a reason to pursue neat alcohol in place of aqueous alcohol in a process for making DCL as claimed by the Applicant. Mere conclusory statements such as “[i]t is known that neat alcohol would be more reactive and efficient than an aqueous solvent . . . The proton transfer is from a neat alcohol is known to faster” are not sufficient. There must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” *In re Kahn*, 441 F. 3d 977 (Fed. Cir. 2006). Indeed, there is evidence to the contrary: (i) a clear pattern exists in the art for producing DCL by reacting loratadine with an aqueous alcohol and/or non-alcoholic solvents as evidenced by a number of references cited by the Examiner; (ii) the proton transfer is faster (in 3 ps or “2 orders of magnitude” higher) in

“aqueous” environment, than in “neat alcohol” (see, Peon at 6436 and Table 2 at 6435) (and hence “aqueous make[s] the fuel cell more efficient and faster”); and (iii) the WO 96 reference suggests the use of acidic hydrolytic conditions, not the basic hydrolytic conditions, for the desloratadine preparation .

In view of this evidence, a person of ordinary skill having the WO 96 reference in hand has no good reason to pursue neat alcohol in place of aqueous alcohol and basic hydrolytic conditions in a process for making DCL and such a pursuit would not lead to the anticipated success. Reconsideration and withdrawal of the rejection based on WO 96 are respectfully requested.

(5) EP ‘855

The EP ‘855 reference discloses a process for making DCL in the presence of aqueous ethanol and caustic in 1:1 ratio. The EP ‘855 reference, however, does not disclose or suggest a process for the production of desloratadine by reacting loratadine with neat alcohol in presence of an inorganic base. The Examiner failed to establish a *prima facie* case of obviousness based on the EP ‘855 reference. Specifically, the Examiner has not provided a sufficient reason or explicit analysis of why a person of ordinary skill has a reason to pursue neat alcohol in place of aqueous alcohol in a process for making DCL as claimed by the Applicant. Mere conclusory statements such as “[i]t is known that neat alcohol would be more reactive and efficient than an aqueous solvent . . . The proton transfer is from a neat alcohol is known to faster” are not sufficient. There must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” *In re Kahn*, 441 F. 3d 977 (Fed. Cir. 2006). Indeed, there is evidence to the contrary: (i) a clear pattern exists in the art for producing DCL by reacting loratadine with an aqueous alcohol and/or non-alcoholic solvents as evidenced by a number of references cited by the Examiner; and (ii) the proton transfer is faster (in 3 ps or “2 orders of magnitude” higher) in “aqueous” environment, than in “neat alcohol” (see, Peon at 6436 and Table 2 at 6435) (and hence “aqueous make[s] the fuel cell more efficient and faster”).

In view of this evidence, a person of ordinary skill having the EP ‘855 reference in hand has no good reason to pursue neat alcohol in place of aqueous alcohol in a process for making

DCL and such a pursuit would not lead to the anticipated success. Reconsideration and withdrawal of the rejection based on EP '855 are respectfully requested.

(6) EP '897

The EP '897 reference discloses a process for making DCL in the presence of aqueous ethanol. The EP '897 reference, however, does not disclose or suggest a process for the production of desloratadine by reacting loratadine with neat alcohol in presence of an inorganic base. The Examiner failed to establish a *prima facie* case of obviousness based on the EP '897 reference. Specifically, the Examiner has not provided a sufficient reason or explicit analysis of why a person of ordinary skill has a reason to pursue neat alcohol in place of aqueous alcohol in a process for making DCL as claimed by the Applicant. Mere conclusory statements such as “[i]t is known that neat alcohol would be more reactive and efficient than an aqueous solvent . . . The proton transfer is from a neat alcohol is known to faster” are not sufficient. There must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” *In re Kahn*, 441 F. 3d 977 (Fed. Cir. 2006). Indeed, there is evidence to the contrary: (i) a clear pattern exists in the art for producing DCL by reacting loratadine with an aqueous alcohol and/or non-alcoholic solvents as evidenced by a number of references cited by the Examiner; and (ii) the proton transfer is faster (in 3 ps or “2 orders of magnitude” higher) in “aqueous” environment, than in “neat alcohol” (see, Peon at 6436 and Table 2 at 6435) (and hence “aqueous make[s] the fuel cell more efficient and faster”).

In view of this evidence, a person of ordinary skill having the EP '897 reference in hand has no good reason to pursue neat alcohol in place of aqueous alcohol in a process for making DCL and such a pursuit would not lead to the anticipated success. Reconsideration and withdrawal of the rejection based on EP '897 are respectfully requested.

(7) '716 patent

The '716 patent discloses a process for making DCL in the presence of aqueous ethanol and caustic in 1:1 ratio. The '716 patent, however, does not disclose or suggest a process for the production of desloratadine by reacting loratadine with neat alcohol in presence of an inorganic

base. The Examiner failed to establish a *prima facie* case of obviousness based on the ‘716 patent. Specifically, the Examiner has not provided a sufficient reason or explicit analysis of why a person of ordinary skill has a reason to pursue neat alcohol in place of aqueous alcohol in a process for making DCL as claimed by the Applicant. Mere conclusory statements such as “[i]t is known that neat alcohol would be more reactive and efficient than an aqueous solvent . . . The proton transfer is from a neat alcohol is known to faster” are not sufficient. There must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” *In re Kahn*, 441 F. 3d 977 (Fed. Cir. 2006). Indeed, there is evidence to the contrary: (i) a clear pattern exists in the art for producing DCL by reacting loratadine with an aqueous alcohol and/or non-alcoholic solvents as evidenced by a number of references cited by the Examiner; and (ii) the proton transfer is faster (in 3 ps or “2 orders of magnitude” higher) in “aqueous” environment, than in “neat alcohol” (see, Peon at 6436 and Table 2 at 6435) (and hence “aqueous make[s] the fuel cell more efficient and faster”).

In view of this evidence, a person of ordinary skill having the ‘716 patent in hand has no good reason to pursue neat alcohol in place of aqueous alcohol in a process for making DCL and such a pursuit would not lead to the anticipated success. Reconsideration and withdrawal of the rejection based on the ‘716 patent are respectfully requested.

(8) HU ‘864

The HU ‘864 reference discloses a process for making DCL in the presence of aqueous ethanol. The HU ‘864 reference, however, does not disclose or suggest a process for the production of desloratadine by reacting loratadine with neat alcohol in presence of an inorganic base. The Examiner failed to establish a *prima facie* case of obviousness based on the HU ‘864 reference. Specifically, the Examiner has not provided a sufficient reason or explicit analysis of why a person of ordinary skill has a reason to pursue neat alcohol in place of aqueous alcohol in a process for making DCL as claimed by the Applicant. Mere conclusory statements such as “[i]t is known that neat alcohol would be more reactive and efficient than an aqueous solvent . . . The proton transfer is from a neat alcohol is known to faster” are not sufficient. There must be some articulated reasoning with some rational underpinning to support the legal conclusion of

obviousness.” *In re Kahn*, 441 F. 3d 977 (Fed. Cir. 2006). Indeed, there is evidence to the contrary: (i) a clear pattern exists in the art for producing DCL by reacting loratadine with an aqueous alcohol and/or non-alcoholic solvents as evidenced by a number of references cited by the Examiner; and (ii) the proton transfer is faster (in 3 ps or “2 orders of magnitude” higher) in “aqueous” environment, than in “neat alcohol” (see, Peon at 6436 and Table 2 at 6435) (and hence “aqueous make[s] the fuel cell more efficient and faster”).

In view of this evidence, a person of ordinary skill having the HU ‘864 reference in hand has no good reason to pursue neat alcohol in place of aqueous alcohol in a process for making DCL and such a pursuit would not lead to the anticipated success. Reconsideration and withdrawal of the rejection based on HU ‘864 are respectfully requested.

B. Discussion of the Rejection based on (1) WO 95, (2) Iwasaki, (3) Sejas, (4) WO 96, (5) EP ‘855, (6) EP ‘897, (7) ’716 patent and (8) HU ‘864 in view of Peon

Each of the cited references (1) WO 95, (2) Iwasaki, (3) Sejas, (4) WO 96, (5) EP ‘855, (6) EP ‘897, (7) ’716 patent and (8) HU ‘864 have been discussed above. These references either alone or in combination does not teach or suggest the claimed desloratadine process.

Peon does not cure the deficiencies in the references (1) WO 95, (2) Iwasaki, (3) Sejas, (4) WO 96, (5) EP ‘855, (6) EP ‘897, (7) ’716 patent and (8) HU ‘864 for it does not teach or suggest a process for the production of desloratadine by reacting loratadine with neat alcohol in presence of an inorganic base. Applicant respectfully submits again that the rejection on obviousness grounds cannot be sustained by mere conclusory statements (e.g., the statement that “[t]he Peon reference is used just to validate the point even further” made at page 2 of this Office Action, or that “[u]sing neat alcohol instead of aqueous make the fuel cell more efficient and faster according to Peon Jorge et al.,” made at page 3 of the previous office action of December 19, 2007). The Examiner appears to have misconstrued the Peon reference. Peon does not teach or suggest that using neat alcohol instead of aqueous makes the fuel cell more efficient and faster. It reports that protonation fraction decreases from methanol to 2-propanol due to decreased branching ratio for protonation in the less acidic alcohols. The abstract concludes that “[s]inglet carbenes are powerful, photogenerated bases that open new possibilities for

fundamental studies of proton transfer in solution.” Neither the title nor the description in this reference suggests anything about a process of making desloratadine from loratadine in the presence of a neat alcohol. Peon is about protonation of diphenylcarbene in singlet state and rate of protonation in alcohols.

To the extent the Examiner wishes to continue to rely on Peon for establishing obviousness based on the argument that “[u]sing neat alcohol instead of aqueous make the fuel cell more efficient and faster,” this argument too should fail because Peon suggests just the opposite. See, Peon at 6436 where it teaches that

The fastest known photoacids transfer a proton to a water molecule in slightly less than 10 ps. Excited-state proton transfer to H₂O occurs in 8 ± 1 ps at 25 °C for 5-cyano-1-naphthol . . . and in 7.1 ps for 7-hydroxy-4-methylflavylium . . . Proton transfer from excited 8-hydroxypyrene-1,3,6-trisulfonate to acetate ion, which is present at high concentration in aqueous solution, occurs in 3 ps . . . Ph₂C, which accepts a proton in 9 ps in neat methanol . . . Interestingly, proton transfer to methanol by 5-cyano-1-naphthol is nearly 2 orders of magnitude slower than in water, requiring 390 in CH₃OH.

For ethanol and propanol, the “ps” is even higher than that for methanol. See Peon, Table 2 at 6435. It is clear that the proton transfer is faster (in 3 ps or “2 orders of magnitude” higher) in “aqueous” environment, than in “neat alcohol” (and hence “aqueous make[s] the fuel cell more efficient and faster”). Thus, Peon clearly teaches contrary to the Examiner’s characterization of the reference. In view of this teaching, the motivation for using aqueous alcohol rather than a neat alcohol in a process for making the process more efficient is clearly provided. A person of ordinary skill has good reason to pursue aqueous alcohol, not neat alcohol in a process for making DCL. For these reasons, a person of ordinary skill in the art cannot predictably arrive at the claimed desloratadine process all of (1) WO 95, (2) Iwasaki, (3) Sejas, (4) WO 96, (5) EP ‘855, (6) EP ‘897, (7) ’716 patent and (8) HU ‘864 in view of Peon. Reconsideration and withdrawal of the rejection based on the combination of (1) to (8) and Peon are respectfully requested.

C. Discussion of the Rejection based on US Patent 5595997 (the ‘997 patent)

The Examiner maintained the rejection based on the '997 patent based on the grounds stated at pages 3-4 of the Office Action. Applicant respectfully traverses this rejection.

First, Applicant maintains all of its arguments against the '997 patent made in the paper dated April 21, 2008 filed in response to the previous office action of December 19, 2007. Further, Applicant respectfully believes that this rejection has been overcome in view of the discussion herein.

Applicant agrees with the Examiner in that the transitional term "comprising" in a method claim indicates that the claim is open-ended and allows for additional steps. It also means that the recited steps are essential, but other steps may be added. Claim 1, as clarified, recites as follows:

An improved process for the production of desloratadine which comprises,

- (a) reacting starting compound loratadine with neat alcohol in presence of inorganic base,
- (b) adding excess water after completion of said reaction in step (a);
- (c) isolating the desloratadine in substantially pure crystalline form by conventional methods on addition of excess water in step (b).

In the logical sequence of steps (a)-(c), water is added in step (b) after step (a). The next step is isolation. There is no removal of the neat alcohol as contended by the Examiner. Instead, the desloratadine is isolated in substantially pure crystalline form. The '997 patents explicitly requires that the reaction mixture be cooled and concentrated to remove ethanol before proceeding further only to obtain 87% pure loratadine derivative as a pale-tan solid.

With regard to the type of product, the Examiner contends that "[l]imitation in the specifications cannot be read into the claims. However, it is clear from the summary of the invention and detailed description of the invention and examples that the invention is about an improved process where desloratidine obtained is substantially pure (see, for example, the specification at page 7, lines 1-5, Examples 1-12 and Table 1. The purity of desloratidine obtained, according to the data in Table 1, can be over 99% though less than 100% pure. The claim clarified recites that the desloratadine obtained is substantially pure. Applicant respectfully submits that the term "substantially" is a descriptive term commonly used in patent

claims (*Ecolab, Inc., v. Envirochem, Inc.*, 264 F.3d 1358 (Fed. Cir. 2001)) and the recitation of the term “substantially pure” when considered in light of entire claimed invention is as accurate as subject matter permits, and it provides sufficient guidance to one skilled in the art.

In maintaining the rejection based on the ‘997 patent, the Examiner also appears to contend that it is incorrect to say that Applicants reaction is faster because “Example 6 was completed in 50 hrs. Example 2 was carried out in 12 hours.” Applicant respectfully again draws the Examiner’s attention to column 11, lines 6-14, where it states that “. . . the mixture was stirred at reflux for four days . . .” The process which is nowhere completion requires “four days.” Out of the 12 Examples, Example 6 has the longest time 50 hrs (2 days 2 hours) for completion, which is significantly faster than a process that requires “four days” to complete just the first of the multi-step prior art process in the ‘997 patent. There is nothing incorrect other than the Examiner’s conclusory statement. To support a rejection under 35 U.S.C. § 103, there must be a clear articulation of the reasons why the claimed invention would have been obvious. The Examiner has not provided a sufficient reason or explicit analysis of why the cited prior art references should be modified so as to arrive at the claimed invention. The Examiner cannot impermissibly use the instant claims as a guide or roadmap in formulating the rejection. Therefore, the Examiner’s obviousness rejection is believed to stand in error.

In view of the foregoing, Applicant respectfully submits that the Examiner has not established a *prima facie* case of obviousness of the independent claim 1 under 35 U.S.C. § 103(a). Even if *prima facie* obviousness has been established, which it has not, it is urged that the cited art nonetheless fails to render the present invention obvious under a proper § 103 analysis, as the proper suggestions and motivations are lacking in the cited reference.

Applicant also submits that the Examiner has not established a *prima facie* case of obviousness of dependent claims 2-20 under 35 U.S.C. § 103(a). The rejected dependent claims 2-20, by virtue of their dependency (either directly or indirectly) from the independent claim 1 are similarly considered by Applicant to patentably define themselves over the cited reference. Reconsideration is respectfully requested.

III. Conclusion

Applicant believes this response to be a full and complete response to the Office Action. Accordingly, favorable reconsideration in view of this response and allowance of all of the pending claims are earnestly solicited.

If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Date: December 5, 2008

Respectfully submitted,


Nanda P.B.A. Kumar
Registration No. 44,853
Attorney for Applicant
REED SMITH LLP
2500 One Liberty Place
1650 Market Street
Philadelphia, PA 19103-7301
Telephone: (215) 241-7991
Facsimile: (215) 851-1420